The Three Amnesias

Russell M. Bauer, Ph.D.

Department of Clinical and Health Psychology

College of Public Health and Health Professions

Evelyn F. and William L. McKnight Brain Institute

University of Florida

PO Box 100165 HSC

Gainesville, FL 32610-0165 USA

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During the past five decades, our understanding of memory and its disorders has increased dramatically. In 1950, very little was known about the localization of brain lesions causing amnesia. Despite a few clues in earlier literature, it came as a complete surprise in the early 1950's that bilateral medial temporal resection caused amnesia. The importance of the thalamus in memory was hardly suspected until the 1970's and the basal forebrain was an area virtually unknown to clinicians before the 1980's. An animal model of the amnesic syndrome was not developed until the 1970's.

The famous case of Henry M. (H.M.), published by Scoville and Milner (1957), marked the beginning of what has been called the "golden age of memory". Since that time, experimental analyses of amnesic patients, coupled with meticulous clinical description, pathological analysis, and, more recently, structural and functional imaging, has led to a clearer understanding of the nature and characteristics of the human amnesic syndrome. The amnesic syndrome does not affect all kinds of memory, and, conversely, memory disordered patients without full-blown amnesia (e.g., patients with frontal lesions) may have impairment in those cognitive processes that normally support remembering. It is now known that the amnesic syndrome can follow damage to three major functional systems of the brain: the medial temporal lobe memory system centering on the hippocampus (Milner, 1972; Squire & Zola-Morgan, 1991), the diencephalon (Aggleton, 1986; Butters, 1981; Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990), and the basal forebrain (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985; DeLuca & Diamond, 1995; Hashimoto, Tanaka, & Nakano, 2000). In this chapter, I review the characteristics and anatomic bases for these "three amnesias". Are these three different disorders, or are they variations on a core amnesic syndrome? I will consider this question in a concluding section.

1. Clinical Characteristics of the Amnesic Syndrome

The term "amnesic syndrome" has been used to refer to patients with profound inability in day-to day remembering and varying degrees of remote or retrograde memory impairment whose memory-related disability exists in the context of generally spared cognitive and intellectual function.

1.1 **Anterograde Amnesia.** The hallmark of the amnesic syndrome is a profound defect in new learning called *anterograde amnesia*. The deficit involves "recent" or "long-term" memory; the essential feature of the deficit is that that patient is impaired in the conscious, deliberate recall of information initially learned after illness onset. The defect is apparent in practically any situation in which the recall burden exceeds the immediate memory span, or in which a substantial delay ensues between information exposure and the memory test. Amnesic patients are severely impaired in their daily functioning and their learning deficit is apparent on even casual observation. That is, the deficit is more than just a “memory problem”. Such patients may fail to recognize or learn the names of newly encountered persons after even brief delays. They may appear disoriented in place or time because they have failed to learn their location or have lost the ability to monitor and keep track of ongoing events. Amnesic patients are frequently capable of tracking routine conversation, but their deficit becomes obvious when they are asked to recall an event that occurred only hours or minutes before. Instructions to remember such events for later recall rarely result in measurable improvement. Formal neuropsychological assessment is not needed to reveal the deficit, but such assessment often helps in characterizing the deficit in quantitative and qualitative terms (Squire & Shimamura, 1986).

1.2. **Retrograde Amnesia and Remote Memory Disturbance**

The amnesic patient usually also has difficulty in recalling information learned prior to illness onset, an impairment that is often worse for relatively recent events than for events that occurred in the very remote past. The deficit usually involves both "autobiographical" memories of the patient's specific past (e.g., the circumstances surrounding an important relative's death), and memory for "public" information that has not been personally encountered (e.g., details regarding the recent war in Iraq). Kapur (1999) suggests that autobiographical memory for past personal events is both anatomically and functionally distinct from remote semantic knowledge and fact memory, and some case studies and experimental work supports this distinction. Autobiographical defects are commonly seen after lesions to

the medial temporal and diencephalic structures, while defects in remote semantic memory result more commonly from neocortical damage.

Three patterns of remote memory impairment have been described in the literature. *Temporally limited remote memory disturbance is* an impairment that primarily involves the few years prior to the onset of amnesia with relative sparing of more remote time periods. This has been documented in the amnesic patient H.M. (Corkin, 1984; Marslen-Wilson and Teuber, 1974; Milner, Corkin, & Teuber, 1968), in patients receiving electroconvulsive therapy for depression (Squire et al., 1975; Squire & Fox, 1980) and in recent cases of remote memory impairment after language-dominant temporal lobectomy (Barr, Goldberg, Wasserstein, & Novelly,1990). This deficit pattern has been explained as a failure of consolidation. *Temporally graded remote memory disturbance* affects all time periods, with greater impairment of memories in the recent past. This pattern is said to be typical of patients with alcoholic Korsakoff's syndrome (Albert, et al., 1979; Cohen & Squire, 1981; Meudell, et al., 1980; Seltzer & Benson, 1974; Squire & Cohen, 1984; Squire et al., 1989a), and has also been reported in patients with basal forebrain damage (Gade, 1990). At least in Korsakoff's patients, an increasingly severe anterograde learning deficit associated with years of heavy drinking, coupled with an acute decade-nonspecific deficit coincident with the onset of Wernicke's encephalopathy, have been invoked to explain the temporally graded pattern. *Nonspecific, or pervasive remote memory disturbance* affects all time periods equally, has been described in patients surviving herpes simplex encephalitis (Butters, et al., 1984; Cermak & O'Connor, 1983; Damasio, et al., 1985; Kopelman, 1999) and in certain other amnesic subjects (Sanders & Warrington, 1971) as well as in patients with Huntington's disease (Albert, et al., 1981). This decade-nonspecific pattern has been primarily attributed to a retrieval deficit that impairs access to information from all time periods equally.

1.3 **Other Characteristics of the amnesic syndrome**

Despite significant impairments in new learning and remote memory, amnesics often perform

normally or near-normally on psychometric tests of intelligence (e.g., Wechsler Scales) and on measures of immediate memory, provided that the amount of information is within their attention span (Drachman & Arbit, 1966). Thus, amnesia cannot be explained on the basis of poor attention span or generalized intellectual loss. However, other cognitive deficits can be seen in some amnesic patients, and may contribute to their deficits in memory. Examples include visuoperceptual and executive skills deficits in alcoholic Korsakoff's syndrome (Kapur and Butters, 1977; Kopelman, 1995; Moscovitch, 1982; Squire 1982b) and prominent frontal lobe-executive deficits in patients with basal forebrain amnesia (DeLuca & Diamond, 1995).

Remarkably, even densely amnesic patients show certain spared memory capacities. When memory is indexed indirectly by changes in performance rather than by direct, explicit, conscious recollection, amnesics often show normal or near-normal performance. These intact capabilities are reflected, for example, in (a) the acquisition of new motor, perceptual, and cognitive skills (Beaunieux, et al., 1998; Cohen & Squire, 1980; Cohen, Poldrack, & Eichenbaum, 1997; Schmidtke, Handschu, & Vollmer, 1996), (b) the intact facilitation ("priming") of performance (as measured by increased accuracy or response speed) when specific stimuli, or stimulus contexts, are repeated after initial presentation (e.g., Cermak, Talbot, Chandler, & Wolbarst, 1985; Gabrieli, Milberg, Keane, & Corkin, 1990; Hamann & Squire, 1997), and (c) intact “non-cognitive” forms of learning such as classical conditioning in some amnesics but not others (Gabrieli et al., 1995; Myers et al., 2001; Schugens & Daum, 1999; Woodruff Pak, 1993).

2 Anatomic correlates of amnesia

As indicated above, the amnesic syndrome can result from focal damage to the medial temporal lobes, the medial thalamus, or the basal forebrain. Anatomic, physiologic and behavioral studies in non-human primates have suggested why these regions may be important for memory. An understanding of the underlying circuitry provides a basis for considering these three regions not as discrete entities, but as

parts of an integrated, distributed, memory system.

2.1 **Temporal lobe.**

The importance of the temporal lobes in memory was established in the 1950's by reports of severe and permanent amnesia after bilateral resections of the medial aspects of the temporal lobes in humans (Scoville, 1954; Scoville and Milner, 1957). The aim of surgery was either to ameliorate psychotic behavior or to treat intractable epilepsy. H.M., who was treated for epilepsy, is the best studied of such patients, having been the subject of numerous reports over nearly five decades.

H. M.'s intended lesions extend 8 to 9 centimeters back from the temporal poles, and include the amygdala, the hippocampus, and the parahippocampal region. An appreciation of the anatomic connections of these regions is necessary to understand their role in memory function.

2.1.1. The hippocampus and parahippocampal region

The hippocampus is a phylogenetically ancient cortical structure consisting of the dentate gyrus, the sectors of Ammon's horn (cornu Ammonis (CA) 1-4), and subiculum. The internal connections of the hippocampus were identified by Ramón y Cajal and his student Lorrente de Nó (cited by Van Hoesen, 1985), who first described the *trisynaptic circuit.* Neurons of the entorhinal cortex project via the *perforant pathway* to synapse on dendrites of granule cells in the dentate gyrus. Granule cell axons project to the dendrites of pyramidal cells in the CA3 region of Ammon's horn (*mossy fiber projection*). These pyramidal cells have axons that bifurcate, one branch projecting subcortically via the fimbria fornix, and the other (*Shaffer collateral pathway*) to CA1. CA1 neurons project subcortically via the fimbria, but also to the subiculum, which is the major source of hippocampal efferent projections (Rosene & Van Hoesen, 1977). Efferent fibers from the subiculum project either to subcortical targets (via the fimbria and fornix) or to other cortical regions. The subiculum also projects back to the entorhinal cortex, completing a circuit. The connections described are unidirectional, suggesting an orderly progression of information through the hippocampus.

Although there are direct cortical connections to the hippocampus proper, the majority of hippocampal cortical connections are with the adjacent parahippocampal region. The parahippocampal region consists of rhinal (entorhinal and perirhinal) cortex, pre- and para-subicular cortex, and parahippocampal cortex (Scharfman et al., 2000). The parahippocampal region is hierarchically organized, with the entorhinal cortex being the final common pathway to the hippocampus (Van Hoesen and Pandya, 1975). The entorhinal cortex receives afferents from perirhinal cortex and the parahippocampal gyrus (Insausti, Amaral & Cowan, 1987a; Irle & Markowitsch, 1982; Rosene & Van Hoesen, 1977; Van Hoesen, Rosene & Mesulam, 1979). These regions in turn receive projections from unimodal and polymodal association cortex, thus providing entorhinal cortex with indirect access to a variety of highly processed information (Amaral, Insausti & Cowan, 1983; Insausti, Amaral & Cowan, 1987a; Van Hoesen, 1985; Van Hoesen, Pandya & Butters, 1972). Unlike the intrinsic hippocampal connections, which are unidirectional, the connections of the parahippocampal region are reciprocal (Rosene & Van Hoesen, 1977). Both perirhinal and parahippocampal cortices are connected with visual and polymodal cortical regions, and, to a lesser extent, with somatosensory cortex; but only the parahippocampal cortex receives substantial input from parietal polysensory and auditory cortices (Suzuki & Eichenbaum, 2000).

Subcortical projections from the hippocampus travel in the fornix, a white matter structure that arches through the lateral ventricle and descends medial to the foramen of Munro into the lateral wall of the third ventricle, where it divides at the anterior commissure. Fibers from CA1, CA3 and the subiculum project in the pre-commissural fornix to the lateral septal nucleus (Swanson & Cowan, 1979). Other subicular projections travel in the post-commissural fornix and terminate in either the anterior nuclear complex of the thalamus or the mammillary bodies (Swanson & Cowan, 1979; Van Hoesen, 1985). There are also hippocampal projections to the amygdala, nucleus accumbens and other regions in the basal forebrain, and to the ventromedial hypothalamus (Amaral & Insausti, 1990; Swanson & Cowan, 1979).

The hippocampal → post-commissural fornix → mammillary body projection was part of the "circuit" described by Papez in 1937 to explain how emotional expression and feeling, mediated by the hypothalamus, could be coordinated with cognition, mediated by the cortex. The hippocampus projects via the post-commissural fornix to the mammillary bodies, which, in turn, project via the mammillothalamic tract to the anterior nuclei of the thalamus. The circuit, which has since been referred to as the "medial limbic circuit", is completed by thalamic projections to the cingulate gyrus and cingulate projections, via the cingulate bundle or cingulum, which extend back to the hippocampus.

The hippocampus also receives subcortical projections from the basal forebrain (medial septal nucleus and the nucleus of the diagonal band of Broca), from midline, anterior, and laterodorsal thalamic nuclei, and from amygdala, hypothalamus, and brainstem, including the central gray, ventral tegmental area, raphé nuclei and locus coeruleus (Amaral & Cowan, 1980; Amaral & Insausti, 1990; Herkenham, 1978; Insuasti, Amaral & Cowan, 1987b; Van Hoesen, 1985).

2.1.2. **The amygdala**

The amygdala is situated immediately anterior to the hippocampus, and deep to the periamygdaloid and perirhinal cortices. It has two main parts: a large basolateral group of nuclei, with extensive connections to limbic and association cortex and to dorsomedial thalamus, and a smaller corticomedial segment, which extends into the basal forebrain and has extensive connections with basal forebrain, hypothalamus, and brainstem (DeOlmos, 1990; Heimer & Alheid, 1991; Scott, DeKosky & Scheff, 1991). In a very general sense, the connections of amygdala and hippocampus are similar: both are strongly interconnected with frontal and temporal limbic cortex, and thus both have indirect access to polymodal and supramodal neocortical association areas (Herzog & Van Hoesen, 1976; Rosene & Van Hoesen, 1977). Both project to basal forebrain and hypothalamus. The amygdala and hippocampus also have direct connections with each other (Insuausti, Amaral & Cowen, 1987b; Poletti, 1986; Saunders, Rosene & Van Hoesen, 1988).

But there are also striking anatomic differences. Although in the brains of higher mammals the amygdala is adjacent to the hippocampus, it differs radically from the hippocampus in structure and derivation. The amygdala is a subcortical structure, intimately related with the basal forebrain, and often classified as one of the basal ganglia. The amygdala is more closely related to limbic and neocortical regions that are of paleocortical derivation, whereas the hippocampus is archicortical, and is more closely related to cortex of archicortical derivation (Pandya & Yeterian 1990). Thus, the amygdala is more closely related to orbitofrontal and anterior temporal cortex (Porrino, Crane & Goldman-Rakic, 1981), and the hippocampus is more closely related to cingulate cortex. Abnormalities in emotional responsiveness and social interactions are associated with lesions in the amygdala and related anterior temporal and orbitofrontal cortex (Butter & Snyder, 1972).

The subcortical connections of the amygdala also differ from those of the hippocampus. Whereas the hippocampus is related through Papez' medial limbic circuit with the mammillary bodies and the anterior thalamic nuclei, the amygdala has projections (via the ventral amygdalofugal pathway) to the dorsomedial nucleus of the thalamus (Nauta, 1961). Basal forebrain connections also differ: the hippocampus is related to more ventral portions of the septal nuclei, and the amygdala has more extensive connections with the bed nucleus of the stria terminalis. Cholinergic projections to the amygdala are from the nucleus basalis of Meynert, whereas the hippocampus receives input from the septal region and diagonal band of Broca (Mesulam et al., 1983). Finally, the amygdala has connections with brainstem autonomic centers (nucleus of the tractus solitarius), providing a direct pathway for limbic-autonomic interaction. In contrast to Papez' medial limbic circuit, the amygdala can be thought of as participating in a "lateral" limbic circuit: amygdala → dorsomedial nucleus of the thalamus → orbitofrontal cortex → uncus → amygdala.

2.1.3. **The anatomical basis of temporal lobe amnesia.**

Early studies of patients with bilateral temporal lobectomy supported the idea that damage to the

hippocampus was necessary for medial temporal lesions to produce amnesia. Scoville and Milner (1957) reviewed ten patients with bilateral medial temporal resections. Removal of the uncus and amygdala (in one patient) caused no memory loss, but resections that extended posteriorly to involve the hippocampus and parahippocampal gyrus were associated with amnesia. Also, amnesia was more severe with more extensive resections. Scoville and Milner concluded that amnesia would not occur unless the surgery extended far enough back to involve the hippocampus.

The case for the importance of the hippocampus in memory was subsequently made even more convincingly by the study of patients who survived cardiopulmonary arrest with well-documented deficits in memory, and whose brains were examined after they died from other causes (Cummings et al., 1984; Victor & Agamanolis, 1990; Zola-Morgan, Squire & Amaral, 1986). In each case, damage was restricted almost entirely to the hippocampus, where the pyramidal neurons of CA1, exquisitely sensitive to hypoxia, were selectively destroyed. Global ischemia in monkeys causes similar lesions, with scores on memory tasks comparable to those of monkeys with surgical lesions restricted to the hippocampus (Squire & Zola-Morgan, 1991). It should be noted that in these cases, memory loss was not as severe as that seen in H.M.

Our basic understanding of the anatomic substrate of temporal lobe amnesia was greatly enhanced in the 1970's by the development of animal models of amnesia. This advancement was facilitated by the development of tasks, including delayed matching-to-sample (DMS; Gaffan, 1974) and delayed nonmatching-to-sample (DNMS; Mishkin, 1978) that provided meaningful analogues to human memory paradigms. DNMS was learned more readily than DMS by normal monkeys, who presumably were drawn to novelty. Hundreds of different objects were used so that habits (or "familiarity") could not be used as a basis for recognition. Monkeys with extensive medial temporal lesions, involving both amygdala and hippocampus, were more impaired on the DNMS task than were monkeys with damage to the hippocampus or amygdala alone.

This critical observation led to the hypothesis that *two parallel systems subserve memory, one involving the hippocampus and the other the amygdala* (Mishkin, 1978; Mishkin and Saunders, 1979; Mishkin, 1982; Mishkin et al., 1982). Because either system can subserve memory in large part, lesions in both systems are required to produce severe amnesia. This has come to be known as the "***dual system theory of amnesia***", and forms a core principle of understanding memory disorders regardless of lesion location. In a series of experiments, Mishkin and colleagues extended their observations to the subcortical projections of these two medial temporal structures, focusing on the circuits (medial and lateral limbic circuits) described above and in Figures 1and 2.

Figure 1 about here

The basic principle is that ***amnesia occurs when both the lateral and medial limbic circuit are damaged*** (we will see later that this principle explains most diencephalic and basal forebrain amnesias as well; Figure 2 depicts the basic anatomy of memory with a rudimentary representation of the basal forebrain contributions to the two limbic circuites added). Thus, for example, lesions that interrupt both the fornix (disrupting Papez' circuit) and the ventral amygdalofugal pathways (disrupting the lateral circuit) cause severe amnesia, whereas lesions restricted to either pathway alone cause less memory disturbance (Bachevalier, Saunders & Mishkin, 1985; Bachevalier, Parkinson & Mishkin, 1985). Many other combinations on this general theme are possible and have been documented in the literature.

Figure 2 about here

Lesions that affect either the posteromedial or anteromedial aspect of the thalamus cause little memory disturbance; but severe amnesia, comparable to that associated with medial temporal ablations,

occurs only when *both* anterior and posterior medial thalamic regions are involved (Aggleton & Mishkin, 1983). Finally, lesions that affect the frontal projections of both Papez' circuit (anterior cingulate gyrus) and the lateral circuit (ventromedial frontal lobe) produce greater memory loss than lesions of either alone (Bachevalier & Mishkin, 1986). This series of studies on primates suggests (1) that structures within each memory system are highly interdependent, since damage to different parts of each system can cause apparently equivalent deficits; and (2) that each system can, to a large extent, carry on the function of the other, since lesions affecting only one system result memory loss that is far less severe than if both systems are damaged.

This theory had to be modified when it was demonstrated that collateral damage to the perirhinal cortex was responsible for the memory deficits seen after amygdala lesions. Stereotactic lesions of the amygdala sparing perirhinal cortex do not add to the memory deficit of animals with hippocampal and parahippocampal gyrus lesions (Zola-Morgan, Squire & Amaral, 1989a). Zola-Morgan et al (1989b) found that lesions involving both perirhinal and parahippocampal cortex but not the hippocampus cause severe memory impairment in the monkey. This is not explained entirely by interruption of cortical input to the hippocampus, because monkeys with this lesion had *more* severe memory deficits than monkeys with lesions that only involved the hippocampus and parahippocampal gyrus (Zola-Morgan & Squire, 1986; Squire & Zola-Morgan, 1991). Similar findings were reported by Meunier et al. (1993). This suggests that the perirhinal cortex not only conveys information to the hippocampus via entorhinal cortex, but that it contributes to memory in its own right. Because both the amygdala and the perirhinal cortex project to dorsomedial thalamus, the dual system theory could be easily modified by substituting perirhinal cortex for the amygdala (this connection is signified by the right-most line in Figure 1).

In summary, the temporal lobes play a significant role in memory; however, the relative contribution of different temporal lobe structures remains to be worked out. At this point, one can argue on the basis of animal models that the hippocampus has a particular role in spatial memory, and that

object memory may be more dependent upon perirhinal cortex. It is suggested that the hippocampus in humans may subserve episodic memory, and the perirhinal cortex may be necessary to establish semantic memories. The ability of children with hypoxic damage to the hippocampus to acquire semantic information (Vargha-Kardem et al., 1997) and of amnesic patients to acquire new vocabulary words (Verfaellie, Koseff, & Alexander, 2000) suggests some degree of independence between these kinds of memory; however, there is presently not enough evidence to support a neat anatomic parcellation of these functions. A related distinction between episodic recall and recognition memory is made by Aggelton and Brown (1999), who attribute the former to the hippocampal/diencephalic circuit of Papez, and the latter to the perirhinal cortex and dorsomedial thalamus.

2.1.4. Amnesia from Damage to Other Elements of the Medial Limbic Circuit

Having considered the importance of temporal lobe structures in amnesia, I now turn to consideration of whether amnesia occurs after damage to other components of the medial limbic circuit.

2.1.4.1. Fornix

It was once widely held that surgical section of the columns of the fornix would not result in memory loss (Cairns & Mosberg, 1951; Dott, 1938; Garcia Bengochea et al., 1954; Woolsey & Nelson, 1975), although there was some early evidence to suggest that memory loss might occur (Hassler & Riechert, 1957; Sweet, Talland & Ervin, 1959). Heilman and Sypert (1977), reporting on a case who had a tumor affecting fornix projections, argued that lesions of the fornix posterior to the anterior commissure affect not only fibers destined for the mammillary bodies, but also disrupt connections between the hippocampus and the basal forebrain, and direct projections from the hippocampus to the anterior thalamic nuclei (Aggleton, Desimone & Mishkin, 1986; Veazey, Amaral, & Cogan, 1982). They suggested that section of the columns of the fornix ventral to the anterior commissure might not cause amnesia, as it only affects projections to the mammillary bodies. Fornix damage usually results in some degree of amnesia both in animals (Bachevalier, Parkinson & Mishkin, 1985; Bachevalier, Saunders &

Mishkin, 1985; Carr, 1982; Gaffan, 1993, 1974; Moss, Mahut & Zola-Morgan, 1981; Owen & Butler, 1981) and humans (Aggleton et al., 2000; Calabrese et al, 1995; D'Esposito et al., 1995; Gaffan, Gaffan & Hodges, 1991; Gaffan & Gaffan, 1991; Grafman et al., 1985; McMackin et al., 1995; Moudgil et al, 2000; Park et al., 2000). In primates, fornix damage, like hippocampal lesions, impairs spatial memory and memory for objects in a scene, a paradigm that Gaffan (Gaffan & Parker, 1996) suggests is related to episodic memory. In humans, fornix lesions have been found to affect recall more than recognition (familiarity) memory (Aggleton & Brown, 1999), and to cause anterograde but not retrograde amnesia (but see Yasuno et al., 1999).

2.1.4.2. Mammillary bodies

The anatomy of mammillary body connections is summarized by Aggleton & Sahgal (1993). This paired hypothalamic nucleus receives substantial input from the hippocampus. There are projections from the subicular complex of the hippocampus through the fornix to the medial mammillary nucleus, which is more affected than the lateral mammillary nucleus in Wernicke-Korsakoff disease. There are also hippocampal projections to the lateral mammillary nucleus and tuberomammillary nucleus. These hippocampal-mammillary body connections are not reciprocated. Mamillothalamic projections are also unidirectional. The mammillary bodies also project to the medial septum and midbrain.

The presence of prominent mammillary body damage in Wernicke-Korsakoff syndrome first suggested their importance in memory (Gamper, cited by Victor, Adams & Collins, 1971). Victor, Adams and Collins (1971) examined the mammillary bodies and the dorsomedial thalamic nucleus of 43 alcoholics. Five had had suffered Wernicke's encephalopathy but had recovered without evidence of memory loss; 38 had Wernicke-Korsakoff disease, with persistent amnesia. At autopsy, all had lesions of the mammillary bodies; but only the 38 patients with persistent memory loss had lesions involving the dorsomedial thalamic nucleus. They concluded that memory loss could not be attributed solely to mammillary body damage, but was more likely to be associated with thalamic lesions. Mair, Warrington

and Weiskrantz (1979) and Mayes et al. (1988) each report two cases of Wernicke-Korsakoff syndrome with lesions in the thalamus restricted to a thin band of gliosis adjacent to the third ventricle, that affected the midline nuclei, but not the dorsomedial nucleus. Mair, Warrington and Weiskrantz (1979) suggested that the mammillary body lesions (present in each of these patients) may account for the memory loss. Lesions restricted to the mammillary bodies have not been associated with deficits on DNMS tasks in monkeys (Aggleton and Mishkin, 1985). However, deficits on spatial memory tasks have been reported in monkeys (Parker & Gaffan, 1997) and in rats (Sziklas & Petrides, 1998). Human cases with selective mammillary body lesions are rare. Dusoir et al (1990) reported amnesia in a patient with MR evidence of mammillary body lesions following a penetrating injury from a snooker cue. Loesch et al. (1995) report memory deficits in a patient with a cavernous malformation of the mammillary bodies, and Tanaka et al. (1997) report memory loss with mammillary body damage following removal of a cystic craniopharyngioma. It is difficult to exclude extramammillary lesions in these cases, especially to adjacent portions of the hypothalamus or basal forebrain

2.1.4.3. Anterior thalamic nuclei

The anterior thalamic nuclei consist of anteromedial (am), anteroventral (av), anterodorsal (ad) and lateral dorsal (ld) nuclei. The medial mammillary nucleus projects ipsilaterally to am and av; whereas the lateral mammillary nucleus projects bilaterally to ad (see Aggleton and Sahgal, 1993). The anterior thalamic nuclei also receive a substantial direct projection from the hippocampus. Pre- and parasubiculum project to av, and subiculum to am, and the hippocampus also projects to ld. All of these hippocampal-thalamic projections are reciprocated.

The anterior thalamic nuclei project to the cingulate and retrosplenial cortices, among other locations. The lateral dorsal nucleus projects strongly to retrosplenial cortex, and shows specific degeneration in Alzheimer's disease (Xuereb et al., 1991).

Parker and Gaffan (1997) demonstrated deficits on a delayed matching to place task in monkeys

with anterior thalamic lesions. Ghika-Schmid and Bogousslavsky (2000) report a series of 12 patients with anterior thalamic infarcts all of whom demonstrated anterograde amnesia (verbal with left and non-verbal with right hemisphere lesions) in combination with perseveration, transcortical motor aphasia, apathy, and executive dysfunction. The lesions involved the anterior thalamic nuclei and not the dorsomedial or ventrolateral nuclei. They also extended to involve the mammillothalamic tract and the internal medullary lamina. More often, thalamic lesions in humans associated with severe amnesia spare the anterior thalamic nuclei (see below). DNMS deficits are reported only with more extensive thalamic involvement

2.1.4.4. Cingulate and retrosplenial cortex

The major cortical connections of the anterior thalamic nuclei are with cingulate gyrus. Bachevalier & Mishkin (1986) suggest that combined lesions of orbitofrontal and anterior cingulate cortex in monkeys damages both memory circuits, the orbitofrontal cortex being connected to the lateral limbic circuit, and the anterior cingulate to the medial circuit. But extensive frontal lesions in man (Eslinger & Damasio, 1985) do not typically result in the classical amnesic syndrome. Meunier, Bachevalier & Mishkin (1997) describe a spatial memory deficit in monkeys with anterior cingulate lesions; studies in rats (Aggleton et al., 1995) suggest that this may be due to damage to the underlying cingulate bundle. The anterior cingulate region appears to play a role in initiating movement, in motivation, and in goal-directed behaviors (Devinsky, Morrell & Vogt (1995), but anterior cingulate gyrus lesions have not been associated with amnesia in humans.

The principal projections of the anterior thalamic nuclei, however, are to posterior cingulate cortex, and especially retrosplenial cortex. These cortical regions are also interconnected with the hippocampus. (Morris, Petrides & Pandya. 1999). Lesions in humans that involve retrosplenial cortex can result in a classical amnesic syndrome (Valenstein et al., 1987) but there remains some debate whether the cause of the amnesia is interruption of cingulate/hippocampal connections via the cingulate bundle,

damage to the retrosplenial cortex itself, or damage to hippocampal-thalamic, hippocampal-basal forebrain (septal nuclei) or frontal lobe connections traveling in the fornix (Rudge & Warrington, 1991; von Cramon and Shuri, 1992). Additional cases of amnesia with retrosplenial lesions have been reported in the Japanese literature by Arita et al., 1995; Iwasaki et al., 1993; Katai et al., 1992; Sato et al., 1998, Takayama et al., 1991; and Yasuda et al., 1997). Takahashi et al. (1999) report pure topographic amnesia with a right retrosplenial lesion. Valenstein et al.'s case (1987) was left-sided, and the memory loss was predominately verbal.

2.1.5. Summary of temporal lobe amnesia. The bulk of the evidence reviewed suggests that (a) damage to cortical and subcortical structures within the temporal lobe, whether focal or extensive, can result in amnesia; (b) amnesia most likely results from simultaneous damage to both the hippocampally-based medial limbic circuit and the amygdala-based lateral limbic circuit; and (c) that damage to individual elements of these circuits can result in amnesia provided that it impairs the functional integrity of this distributed memory system.

Figure 3 depicts two possible lesion scenarios for bitemporal amnesia. In Panel A, an extensive lesion affects both hippocampus and amygdala, and their respective connections to the medial and lateral limbic circuits. In Panel B, a more restricted lesion of the perirhinal-parahippocampal (PRPH) region affects intrinsic functioning of this region and impairs its connectivity to amygdala, hippocampus, and dorsomedial thalamus. Both lesions would be expected to result in clinically significant amnesia.

Figure 3 about here

2.2. Thalamic amnesia

Amnesia associated with tumors in the walls of the third ventricle (Foerster & Gagel, 1933; Grünthal, 1939; Lhermitte, Doussinet & Ajuriaguerra, 1937; Sprofkin & Sciarra, 1952; Williams &

Pennybacker, 1954) provided early evidence that medial thalamic structures may be important in memory. The advent of computed tomographic (CT) and magnetic resonance (MR) imaging made it possible to correlate memory deficits with restricted thalamic lesions in patients with thalamic strokes. Although initial reports appeared to confirm evidence from Wernicke-Korsakoff disease (cited above) that dorsomedial thalamic lesions were associated with memory loss, subsequent studies cast doubt upon this. Early reports had suggested that N.A., a patient who became amnesic after a fencing foil passed through his nose into the brain (Teuber, Milner and Vaughan, 1968), had a restricted lesion involving the left dorsomedial thalamic nucleus on CT scan (Squire & Moore, 1979), and that amnesic patients with thalamic strokes had CT evidence of restricted dorsomedial lesions (Bogousslavsky, Regli & Assal, 1986; Choi et al., 1983; Speedie & Heilman, 1982). High-resolution imaging in N.A., however, revealed that his lesion affected not only the ventral aspect of the dorsomedial nucleus, but also severely damaged the intralaminar nuclei, mammillothalamic tract, and internal medullary lamina (Squire et al., 1989). Such lesions impair connectivity between the mammillary bodies and the anterior nucleus, as well as between the amygdala and the dorsomedial nucleus. N.A. also had lesions affecting the post-commissural fornix, mammillary bodies, and the right temporal tip. More restricted lesions in patients with thalamic infarctions suggest that thalamic amnesia best correlates with lesions affecting the internal medullary lamina and mammillothalamic tract (Gentilini, DeRenzi & Crisi, 1987; Graff-Radford et al., 1990; Malamut et al., 1992, Winocur et al., 1984; von Cramon, Hebel and Schuri, 1985). More posterior lesions that involve portions of the dorsomedial nucleus but spare the internal medullary lamina and mammillothalamic tract are not associated with amnesia (Graff-Radford et al., 1990; Kritchevsky, Graff-Radford & Damasio, 1987; von Cramon, Hebel & Schuri, 1985). The modified dual pathway theory described above suggests that severe and lasting amnesia requires disruption of both the medial and lateral limbic circuits. Graff-Radford et al. (1990) provided a clear anatomic demonstration in the monkey of the juxtaposition of these two pathways (the mammillothalamic tract and the ventral amygdalofugal

pathway) in the internal medullary lamina.

Alternative explanations of thalamic amnesia suggest a role for the midline thalamic nuclei. These nuclei have connections with the hippocampus (Amaral & Cowan, 1980; Herkenham, 1978, Insuasti, Amaral & Cowan, 1987b; Van Hoesen, 1985). They are quite consistently damaged in patients with Wernike-Korsakoff disease (Mair, Warrington and Weiskrantz, 1979; Mayes et al., 1988). Another proposal is that thalamic lesions may disconnect thalamic connections with the frontal lobes. Warrington (Warrington and Weiskrantz, 1982; Warrington, 1985) proposed that restricted thalamic lesions found in their cases of Wernicke-Korsakoff disease (Mair, Warrington & Weiskrantz, 1979) might disconnect mediodorsal-frontal connections important for coordinating posterior cortical regions subserving semantic memories with frontal structures that impose cognitive structure upon these memories.

Figure 4 depicts two possible lesion scenarios for diencephalic amnesia. In Panel A, an extensive lesion of the thalamus affecting both anterior and dorsomedial nuclei impairs both circuits. In Panel B, a more restricted lesion, meant to depict pathway disconnection in the internal medullary lamina, affects both the mammillothalamic tract (MTT), an intrinsic component of the medial circuit, and the ventral amygdalofugal (VAF) pathway, a component of the lateral circuit.

Figure 4 about here

2.3. Basal forebrain amnesia.

The basal forebrain is at the junction of the diencephalon and the cerebral hemispheres, and has, at minimum, the following components: the septal area, diagonal band of Broca, nucleus accumbens septi, olfactory tubercle, substantia innominata (containing the nucleus basalis of Meynert), bed nucleus of the stria terminalis, and preoptic area. It is the third major region, after the temporal lobes and diencephalon, to be considered essential for normal memory function in man. It was known for many years that some

patients developed memory loss after hemorrhage from aneurysms, particularly after rupture of anterior communicating artery aneurysms (Linqvist & Norlen, 1966; Talland, Sweet & Ballantine, 1967); however, the pathogenesis of this amnesia was not understood. Several lines of evidence suggested that cholinergic neurons in the basal forebrain were involved in memory. Lewis and Shute (1967) documented a cholinergic projection from the medial septal region of the basal forebrain to the hippocampus. For many years, scopolamine, a centrally-acting anti-cholinergic agent, had been used in obstetrics, in conjunction with analgesics, to induce a "twilight" state, after which women would have little recall of their deliveries. Drachman and Leavitt (1974) demonstrated that normal subjects had difficulty with free recall of words when given scopolamine, and that this effect was reversed by physostigmine, a centrally acting anticholinesterase agent, that prevents inactivation of acetylcholine. Mesulam and Van Hoesen (1976) documented a cholinergic projection from the basal nucleus of Meynert, and in subsequent studies Mesulam and his colleagues (Mesulam et al., 1983; Mesulam and Mufson, 1984) defined the connections of basal forebrain cholinergic neurons. Neurons in the medial septal nucleus and diagonal band of Broca project strongly to the hippocampus, as had been documented by Lewis and Shute (1967). Cholinergic neurons in the substantia innominata (nucleus basalis of Meynert), however, project widely to limbic system and neocortex. In 1981, Whitehouse et al. documented selective loss of neurons in the nucleus basalis of Meynert in patients with Alzheimer's disease. Cell loss in cholinergic neurons of the basal forebrain (Arendt, Bigl, and Arendt, 1983) has also been found in Wernicke-Korsakoff syndrome (Butters, 1985; Butters & Stuss, 1989). All of these lines of evidence suggested a role for the basal forebrain in memory, and more specifically, suggested that the cholinergic projections of the basal forebrain might be of particular importance. In this way, the structures of the basal forebrain can be thought of as key contributors to both the medial and lateral limbic circuits described earlier.

This “cholinergic hypothesis” (Bartus et al., 1985; Kopelman, 1986) has generated a large volume

of research, but the cholinergic hypothesis itself remains to be established (cf. Fibiger, 1991). Cholinergic medication provides a very modest improvement in memory in patients with Alzheimer's disease (Johns et al., 1983; Peters & Levin, 1979; 1982; Thal et al., 1983). It is not surprising, however, that acetylcholine replacement does not have the dramatic effect that dopamine treatment has in Parkinson's disease, since patients with Alzheimer's disease have degeneration in many other areas thought to be of importance in memory, including the target areas of basal forebrain cholinergic projections (the hippocampus, amygdala, and neocortex).

The complexity of basal forebrain anatomy makes it difficult to arrive at firm conclusions about the pathophysiology of amnesia associated with basal forebrain lesions. In addition to structures containing cholinergic neurons, the basal forebrain encompasses pathways and systems that could conceivably participate in memory. The anterior commissure crosses the midline just posterior to the septal nuclei. The columns of the fornix descend through the basal forebrain on their way to the hypothalamus. The ventral amygdalofugal pathway both projects to the basal forebrain and traverses it on its way to the thalamus. Thus basal forebrain lesions, if properly situated, may disrupt one or both of the pathways critical for memory. The medial forebrain bundle, which interconnects brainstem, hypothalamic and forebrain structures, travels through the lateral hypothalamus and the basal forebrain. Noradrenergic and dopaminergic pathways are represented in the median forebrain bundle. The *extended amygdala* refers to groups of neurons within the basal forebrain, including neurons in the bed nucleus of the stria terminalis and portions of the nucleus accumbens septi, that are anatomically considered to be related to the corticomedial amygdala, with which they are laterally confluent (Heimer & Alheid, 1991). The core of the nucleus accumbens and the olfactory tubercle closely resemble the caudate-putamen, and form the *ventral striatum*, which, in turn, projects to the region of basal forebrain beneath the globus pallidus (the *ventral pallidum*). It is not known if these areas contribute to memory function. The *preoptic area* receives projections from amygdala, hippocampus, and other areas of the basal forebrain. It is involved in

self-regulatory and species-specific behaviors (Swanson, 1987). It is unknown if it has a role in memory.

Most basal forebrain lesions reported in human cases of amnesia have been large, and probably affect all or many of the above structures. Often, they also involve areas outside the basal forebrain, such as the orbitofrontal and medial frontal cortices, and the caudate nucleus. Irle et al. (1992) studied 30 patients with brain lesions associated with anterior cerebral artery aneurysm rupture. Severe memory loss was associated with combined lesions in the striatum (caudate) and basal forebrain, whereas lesions restricted to basal forebrain were not associated with memory disturbance. Morris et al. (1992), however, reported a patient with amnesia following removal of a very small glioma in the lamina terminalis, just posterior to the right gyrus rectus. Post-operative MRI scans demonstrated a lesion restricted to the diagonal band of Broca, anterior commissure, nucleus accumbens, and preoptic area. They postulated that destruction of the cholinergic projection to the hippocampus, most of which originates in the nucleus of the diagonal band of Broca, probably accounted for the amnesia, but they could not rule out contributions from other damaged areas. Although the cholinergic hypothesis has been popular, other neurotransmitter pathways (e.g., dopamine) may be of importance, and their contribution to memory remains to be elucidated.

Figure 5 depicts two possible lesion scenarios for basal forebrain amnesia. In Panel A, a large basal forebrain lesion affects both intrinsic information-processing within the basal forebrain as well as cholinergic input and fibers of passage that are components of both the medial and lateral limbic circuits. In Panel B, a more restricted lesion affects the cholinergic inputs to both circuits, thus impairing functional capacity of these two systems simultaneously.

Figure 5 about here

2.4 Summary of the anatomy of memory.

Earlier conceptions that memory was a localized function subserved by a specific structure such as the hippocampus or dorsomedial thalamus have given way to the view that memory is a distributed function of the human brain. The bulk of the evidence suggests that two functionally and anatomically integrated circuits, one involving the hippocampus and the other involving the amygdala form the basis of this distributed system. Amnesia is associated with medial temporal, thalamic, and basal forebrain damage to the extent that such damage either directly or indirectly impairs the functional integrity of these systems. Most existing evidence suggests that functional impairment of both circuits is necessary for full-blown amnesia to occur.

3. Amnesia Subtypes: Similarities and Differences among Amnesics

The view that memory relies on a distributed system suggests the presence of a "core" amnesic syndrome that results when this system is damaged. Nonetheless, the clinical and neuropathologic heterogeneity in amnesics has fueled speculation that profound memory loss following temporal, diencephalic, and basal forebrain damage may represent different *subtypes* of amnesia (Huppert & Piercy, 1979; Lhermitte & Signoret, 1972; Parkin, 1984; Squire, 1981). One key question has been whether these anatomic-descriptive subtypes can be distinguished on neuropsychological grounds. Data on this issue comes from two main sources: studies evaluating rates of forgetting from long-term memory in diencephalic and bitemporal amnesics, and studies evaluating cognitive deficits specific to diencephalic amnesia, particularly Korsakoff's syndrome.

3.1. Rate of Forgetting from Long Term Memory.

Rate of forgetting from long-term memory been commonly assessed in experimental studies of amnesic patients. Using retention intervals from 10 minutes to 7 days, several authors have argued that bitemporal amnesics (e.g., H.M., herpes encephalitic, bilateral ECT) may show a more rapid rate of forgetting than diencephalic amnesics or controls (Huppert & Piercy, 1979; Martone, Butters, & Trauner, 1986; Squire, 1981). In most of these studies, diencephalic patients are given longer stimulus exposures

(in order to counteract an encoding deficit) than do controls or bitemporals in order to achieve comparable recognition performance at the shortest delays. This, coupled with faster forgetting for bitemporals, initially led to the conclusion that bitemporal amnesia involves a defect in "consolidation", while diencephalic amnesia involves an earlier defect in stimulus "registration" or encoding (Huppert & Piercy, 1979; Squire, 1982a; Winocur, 1984). By this reasoning, once the encoding deficit is circumvented by increased exposure to the stimuli, the normal forgetting in diencephalic amnesics has been taken to mean that their consolidation ability is intact, thus distinguishing them from bitemporals.

However, the widely held view that bitemporal amnesia is distinctively characterized by abnormally rapid forgetting has been questioned by the results of more recent studies. One of the problems with the Huppert and Piercy study is that procedures for matching initial recognition levels result in longer study-test intervals in the bitemporal group than in the diencephalic group (Mayes, Downes, Symons, & Shoqeirat, 1994). Freed, Corkin, and Cohen (1987) retested H.M.'s recognition memory over intervals of 10 minutes, 24 hours, 72 hours and 1 week with two recognition paradigms, taking pains to precisely equate his 10-minute recall with that of normals. The first was a modified Huppert and Piercy (1979) rate-of-forgetting paradigm in which H.M. was given increased exposure to pictorial stimuli (10 sec. compared to 1 sec. for controls) and in which yes-no recognition was probed at the four retention intervals. H.M.'s performance was normal after 10 minutes, but dropped significantly below controls after 24 hours and remained at that level through the 1-week recognition probe. The normal controls continued to forget over the entire week such that their recognition performance declined to H.M.'s level, and was not significantly better than his at 72 hours or 1 week. Freed et. al. suggested that their findings indicated a "normal rate of forgetting over a 1-week delay interval", though as Crosson (1992) has indicated, an alternative explanation of these results is that H.M.'s lowest level of performance for the 1-week interval was raised above previous levels reported by Huppert & Piercy (1979) by virtue of additional stimulus exposure. That is, although Freed et al. focused on the equivalence between H.M.

and normals at the 72-hour and 1-week delays, the fact that H.M.'s performance leveled off more rapidly than controls may, in fact, be taken to support, rather than refute, the notion that bitemporal amnesics forget at an abnormally rapid rate (Crosson, 1992). In the second task reported by Freed et al., forgetting rate was assessed at the same intervals by a forced-choice recognition test rather than a yes-no recognition test. On this task, H.M.'s performance was not significantly different from controls at any interval, and in fact was slightly above that of the controls at 72 hours and 1 week. This is a more convincing demonstration that abnormally rapid forgetting does not necessarily characterize bitemporal amnesia.

McKee & Squire (1992) directly compared rate-of-forgetting from long-term memory in bitemporal and diencephalic amnesics equated for amnesia severity. Both groups of amnesics received 8 seconds of exposure to each of 120 target pictures, while normal controls received 1 second of exposure. Ten minutes, 2 hours, and 30-32 hours after study, subjects were tested with four different recognition probes, including human analogues to paradigms (delayed nonmatching to sample, delayed matching to sample) used in the animal literature. There were no group differences for any of the recognition tests at any retention interval.

Thus, although initial studies differentiated bitemporal and diencephalic amnesia on the basis of long-term forgetting rate, recent studies have tended to emphasize the similarities, rather than the differences, in rate of forgetting in these two groups. Recent evidence suggests that rapid forgetting exists in many amnesics and may vary with the extent to which the memory test taps intentional ("recollection") vs. automatic ("familiarity") aspects of memory (Green & Kopelman, 2002). Some recent studies suggest that there may be subtle differences in the shape of the forgetting curve when recognition probes are concentrated in the first 30 minutes, but there is little evidence of substantial differences thereafter (Downes, Holdstock, Symons, & Mayes, 1998; Mayes, Downes, Symons, & Shoqeirat, 1994). McKee & Squire (1992) suggest that, although it is reasonable to suppose that the medial temporal lobe and diencephalic systems should have different contributions to normal memory,

"each region might also be an essential component of a larger functional system such that a similar amnesia might result from damage to any portion of that system."

3.2. Patterns of Retrograde Amnesia

In Section 1.2, three types of retrograde amnesia (temporally-limited, temporally-graded, and nonspecific) were described. These patterns of retrograde amnesia have been attributed at least in part to impairments in consolidation or retrieval that also produce anterograde learning deficits. Squire (1984) initially suggested that temporally limited retrograde amnesia was due to a defect in consolidation specifically related to dysfunction of the hippocampus (Zola-Morgan & Squire, 1990b), thus linking it specifically to bitemporal amnesia. However, Squire, Haist, and Shimamura (1989), using an updated version of Cohen & Squire's (1981) remote faces and events tests, found extensive, temporally limited retrograde amnesia in both Korsakoff patients (n=7) and a group of patients with presumed medial temporal pathology secondary to anoxia or ischemia (n=3). Although there were differences in the specific pattern exhibited by individual patients, their retrograde amnesia spanned a period of about 15 years and was not detectible in the more remote time periods. Gade & Mortensen (1990) found graded retrograde memory loss, supposedly typical of patients with bitemporal amnesia, in patients with basal forebrain and diencephalic amnesia (including five patients with Korsakoff's syndrome). It is thus unlikely that differences in the degree or pattern of retrograde amnesia can reliably distinguish among basal forebrain, diencephalic, or medial temporal amnesics, though there may still be reason to distinguish between temporally graded, temporally limited, and decade-nonspecific patterns in the individual case. Some recent clinical and experimental evidence suggests that the degree and pattern of retrograde deficit may depend on concomitant involvement of temporal (Kapur & Brooks, 1999; Reed & Squire, 1998) or frontal (Kopelman, 1991; Kopelman, Stanhope, & Kingsley, 1999; Winocur & Moscovitch, 1999) *cortex* that is regionally associated with temporal or diencephalic damage per se. Kapur (1999) suggests that, while lesions of the hippocampus and diencephalon can produce limited retrograde amnesia, more

extensive episodic (autobiographical) or semantic (fact-based) retrograde amnesia generally requires neocortical damage. Kapur argues that those cases with extensive retrograde amnesia from ostensibly localized damage must be interpreted in light of the more widespread metabolic effects on brain function that result.

3.3. Deficits in the Spatiotemporal Context of Memory

Several studies have suggested that certain cognitive abilities might be disproportionately impaired in diencephalic amnesia, particularly in patients with alcoholic Korsakoff (AK) syndrome. Early research on AK patients suggested that they may display disproportionate impairments in the spatiotemporal aspects of memory. A critical issue is whether such impairments are an obligatory part of the amnesia seen in these patients, or whether they result from concomitant frontal involvement.

3.3.1. Memory for Temporal Order. The ability to discriminate when a target item occurred in a study sequence is a critical memory function necessary to maintain order in the flow of events (Hirst & Volpe, 1982; Huppert & Piercy, 1976; McAndrews & Milner, 1991). In a typical temporal-order judgment paradigm, subjects are given a list discrimination task in which a target list is initially shown, followed after a brief delay by a second target list. During later testing, subjects are asked whether they had seen each stimulus before (recognition judgment) and, if so, whether it belonged to the first or second list (temporal order judgment). It is now clear that bitemporal and diencephalic amnesics can both show defects in temporal order judgments, but the issue of whether the underlying mechanisms are the same has not been fully resolved (Downes, Mayes, MacDonald, & Hunkin, 2002; Shimamura, Janowsky, & Squire, 1990). In an early study of this phenomenon, Squire, Nadel, & Slater (1981) examined temporal order judgments in bilateral ECT (bitemporal) patients, patient N.A. (diencephalic), and controls. They found that, though impairments in temporal order judgments were seen in both ECT patients and N.A., recognition judgments were also poor. When recognition performance was subsequently equated with normals, no temporal ordering deficit remained. Thus, in

these patient groups, impaired temporal order judgments appeared to be similar and due to poor recognition memory.

However, the impairment in temporal order judgments exhibited by AK patients cannot, in most studies, be accounted for on the basis of their poor recognition performance (Bowers, Verfaellie, Valenstein, & Heilman, 1988; Meudell, Mayes, Ostergaard, & Pickering, 1985; Shuren, Jacobs, & Heilman, 1997; Squire, 1982b; but see Kopelman, 1997). Several authors (Moscovitch, 1982; Schacter, 1987b; Squire, 1982b) have attributed the temporal ordering impairment in these patients to concomitant frontal lobe pathology known to co-exist with diencephalic damage (Jernigan et al., 1991a, 1991b; Shimamura, Janowsky, & Squire, 1990). By this view, impairments in judging temporal order is a "neighborhood sign" rather than a core symptom of amnesia. Indeed, *nonamnesic* patients with frontal lesions and basal ganglia disease show impairment in temporal order judgments (McAndrews & Milner, 1991; Milner, Petrides, & Smith, 1985; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988; Shimamura et al., 1990). Although the link to frontal lobe damage has been relatively consistent, there are two reasons to keep the book open on this issue. First, results from a temporal-ordering study with a retrosplenial amnesic suggest that a defect in temporal ordering can exist independently of both recognition ability and frontal lobe dysfunction (Bowers, Verfaellie, Valenstein, & Heilman, 1988; see also Parkin & Hunkin, 1993). Interestingly, this patient was dramatically impaired in temporal order judgments for newly acquired information, but had no difficulty judging the temporal order of remote events. He performed normally on tests of frontal lobe function, as did another patient with a hypothalamic glioma but no concomitant frontal damage (Parkin & Hunkin, 1993). These findings provide an initial clue that it may be important to distinguish between two kinds of temporal ordering deficits: (1) one which is a part of a more general, frontally-mediated strategic deficit (as in Korsakoff's syndrome; Shimamura et al., 1990; Squire, 1982b), and (2) another which reflects an anterograde impairment in "time tagging" new information that is independent of frontal pathology (Bowers et al.,

1988; Parkin & Hunkin, 1993; Yasuno et al., 1999).

3.3.2. Source Monitoring and Source Amnesia. Successful retrieval from episodic memory has an autobiographical quality and is characterized by direct recollection of both the content and source of remembered information (Johnson, Hashtroudi, & Lindsay, 1993). The phenomenon of *source amnesia* illustrates that the content and source of recollected information are potentially dissociable (Shimamura & Squire, 1987). In source amnesia, recollection of the informational source of a memory item is lost despite intact item (content) memory. For example, we might remember specific information about a book or movie, but be unable to recollect where that information was learned. Source attributions differentiate autobiographical event memories from more general factual knowledge.

Schacter, Harbluck & McLachlan (1984) presented bogus facts (e.g., “Bob Hope's father was a fireman”) to their patients and then gave a recall test. If a fact was recalled, patients were asked where they had learned it. Many patients demonstrated recall of at least some of the facts, but frequently asserted that they had learned them from a source other than the experimental session. This finding could not be explained by poor memory, since normal subjects whose recall was lowered by a 1-week study-test interval did not commit source errors. Shimamura & Squire (1987) taught obscure (true) facts to a small group of Korsakoff patients and a smaller group of patients with amnesia secondary to anoxia. Severe source amnesia, in which recall was attributed to sources other than the experiment, was observed in 3 of the 6 Korsakoff patients and in 1 of the 3 anoxic patients. The level of fact memory performance did not predict the degree of source amnesia. Furthermore, patients with bitemporal amnesia, including H.M., who display severe defects in fact memory, often perform *better* at tests of recency and temporal order than do nonamnesic frontal patients (Milner, Corsi & Leonard, 1991; Sagar et al., 1990).

Some evidence suggests that the severity of source amnesia varies as a function of frontal lobe impairment in amnesic and nonamnesic subjects (Schacter et al., 1984; Janowsky, Shimamura & Squire, 1989). Source monitoring tasks make variable demands on retrieval and cognitive estimation (Shallice &

Evans, 1978), reality-monitoring (Johnson, 1991), attribution (Jacoby, Kelly, & Dywan, 1989), and temporal order memory (Hirst & Volpe, 1982; Olton, 1989). At this point in the development of source-memory evaluation, it is likely that any distinctions between bitemporal and diencephalic amnesics that have emerged are due to the variable demands on these functions imposed by tests of source memory.

3.3.3. Deficits in Metamemory and "Feeling of Knowing."

Another cognitive domain that some have thought to be differentially impaired in alcoholic Korsakoff syndrome has been referred to as *metamemory*. Metamemory involves knowledge about one's own memory capabilities, the memory demands of particular tasks or situations, and potentially useful strategies relevant to given tasks or situations (Flavell & Wellman, 1977; Gruneberg, 1983). It encompasses people's beliefs (e.g., "I will [or will not] be able to remember these words") as well as their knowledge about the memory system (e.g., rehearsal strategies that enhance recall). Hirst & Volpe (cited in Hirst, 1982) were among the first to report differentially impaired metamemory in Korsakoff patients when compared to other etiologies of amnesia. Based on interviews, they found that Korsakoff patients had less knowledge of mnemonic strategies than did patients with amnesia from other causes.

The most widely studied memtamemorial capacity in amnesic patients is the feeling-of-knowing (FOK) phenomenon (cf. Gruneberg & Monks, 1974; Hart, 1965, 1967; Nelson, Leonesio, Shimamura, Landwehr, & Narens, 1982, Nelson, Gerler, & Narens, 1984). In a typical FOK experiment, subjects are asked to freely recall the answers to general information questions of varying difficulty (e.g., "What is the tallest mountain in South America?") until a certain number of failures occur. For these unrecalled items, subjects are then asked to judge the likelihood that they would be able to recognize the correct answer if it was presented along with other likely but incorrect choices. FOK predictions are then validated by a subsequent recognition test. The general finding in normals is that recognition performance is better for questions eliciting strong FOK than for questions eliciting weak or no FOK.

Shimamura & Squire (1986) evaluated the ability of feeling-of-knowing judgments to predict

subsequent recognition performance in patients with Korakoff's syndrome, psychiatric patients undergoing bilateral ECT, a mixed group of amnesics that included N.A., and controls. Using general information questions (Study 1) and a sentence memory paradigm that assessed newly learned information (Study 2), they found that only the Korsakoff patients (and not the other diencephalic cases) displayed impairment in making FOK judgments. From these results, it appears that metamemory dysfunction is not an obligatory aspect of amnesia (or even diencephalic amnesia), since amnesia can occur without any measurable impairment in FOK. The authors speculated that the disturbed FOK in Korsakoff patients might be a function of their frontal pathology, which would be expected to impair their ability on a variety of judgment and planning tasks.

3.4. Basal forebrain amnesia.

Amnesia due to basal forebrain lesions most commonly results from vascular lesion or aneurysm surgery in the region of the anterior communicating artery (Alexander & Freedman, 1983; Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985; DeLuca & Cicerone, 1989; Gade, 1982; Okawa, Maeda, Nukui, and Kawafuchi, 1980; Volpe & Hirst, 1983; Vilkki, 1985; Phillips, Sangalang & Sterns, 1987). After basal forebrain damage, the patient exhibits extensive anterograde but variable retrograde amnesia. Temporal gradients similar to that seen in Korsakoff's syndrome have been described (Gade & Mortensen, 1990; Lindqvist & Norlen, 1966). Some authors have also described impairment in placing memories in proper chronological order (Damasio, Graff-Radford, Eslinger, Damasio & Kassell 1985; Lindqvist & Norlen, 1966; Talland, Sweet & Ballantine, 1967). Free, and sometimes wild, confabulation appears to be characteristic, particularly in the acute period (Alexander & Freedman, 1983; Damasio, et al., 1985; Lindqvist & Norlen, 1966; Logue et al., 1968; Okawa et al., 1980; Talland, et al., 1967) and probably relates to the extent of concomitant orbitofrontal involvement, particularly in those patients who show spontaneous, or unprovoked confabulation (Damasio, et al., 1985; DeLuca & Cicerone, 1989; Fischer, Alexander, D'Esposito, & Otto, 1995; Phillips, Sangalang, & Sterns, 1987; Vilkki, 1985). Some

patients have difficulty distinguishing reality from dreaming. Although these behavioral abnormalities are distinctive, they may not be functionally related to the amnesia per se. Often, basal forebrain amnesia persists after dream-waking confusion and confabulation have subsided (Hashimoto, Tanaka, & Nakano, 2000; Morris, Bowers, Chatterjee, & Heilman, 1992)

Cueing seems to differentially improve memory performance in these patients, and anecdotal evidence suggests that many of these patients can recall specific information in one retrieval attempt, but not the next. These data have led to the general idea that these patients suffer from a problem in accessing information that does exist in long-term memory. However, further data is needed before accepting this proposition confidently. It has frequently been noted that these patients appear apathetic and unconcerned about their memory impairment (Alexander & Freedman, 1983; Phillips, et al., 1987; Talland, et al., 1967). Interestingly, Talland regarded basal forebrain amnesics to show striking behavioral similarities to patients with Korsakoff syndrome, and Graff-Radford et al., (1990) saw similarities between these amnesics and those suffering memory loss secondary to paramedian thalamic infarctions. It may be that such similarities arise because the large, vascular lesions that characterize these cases also involve structures or pathways destined for components of the medial temporal or diencephalic memory systems (Gade, 1982; Crosson, 1992). Although these anatomic considerations are important there is as yet insufficient behavioral data on which to formally compare basal forebrain amnesics with amnesics of diencephalic or bitemporal origin.

4. Conclusion

Four decades of research with amnesic subjects has led to an increased understanding of the role that specific brain regions and brain systems play in normal and disordered memory functions. It could be said that we now have a good understanding of the fundamental components of the brain's distributed memory system, and decades of experience with ammesic patients has led to an increased appreciation of the anatomic and symptomatic heterogeneity within the amnesic population. The focus of the next decade

will likely be on building and testing more comprehensive models of memory function at the network level.

For now, we return to our original question: Are there really "three amnesias" or do the amnesias of medial temporal, diencephalic, or basal forebrain origin represent variations on a "core" amnesic syndrome? In my view, the weight of the current data favors the latter interpretation. To be sure, there are clinically significant differences between these three groups of amnesics, but many of these differences can be attributed to concomitant damage to cortical and subcortical structures adjacent to the integrated memory circuits. Distinctions among patients (and patient groups) on the basis of forgetting rates, encoding v. consolidation deficits, or on the basis of impairments in contextual or metamemorial aspects of memory are important on both clinical and experimental grounds, even though such distinctions do not thus far appear reliably reflective of lesion localization. Although the behavioral distinctions among amnesic subtypes is not that reliable or impressive, it still is reasonable to hypothesize that the different components of the distributed memory system have different functional contributions to memory performance and that such functions can be measured if sufficiently sensitive and specific behavioral probes are developed and implemented in clinical research.

The interdisciplinary study of memory and its disorders is a remarkable success story in neuropsychology and clinical neuroscience. It is thus likely that our understanding of normal and impaired memory will continue to advance dramatically as increasingly sophisticated behavioral paradigms and neurodiagnostic technologies are brought to bear on this critically important area of brain function.

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Figure Captions

Figure 1. The Dual System Theory of Amnesia. The hippocampally-based "medial" system is depicted by solid lines, while the amygdala-based "lateral" system is depicted by dotted lines. Perirhinal-parahippocampal cortex contributes to both systems by projecting to both amygdala and hippocampus, as well as to dorsomedial nucleus of the thalamus (right-most projection in the figure). AC = anterior commisure; LSN = lateral septal nucleus; MTT = mammillothalamic tract; VAF = ventral amygdalofugal pathway; RSA = retrosplenial area; UF = uncinate fasciculus. See text for details.

Figure 2. Dual System with Basal Forebrain Inputs. Not all inputs from the basal forebrain are shown. Abbreviations within the two limbic circuits are as in Figure 1. NBM = nucleus basalis of Meynert; BNst = bed nucleus of the stria terminalis; DBB = diagonal band of Broca; SEP = septal nucleus. See text for details.

Figure 3. Two Possible Lesion Scenarios for Bitemporal Amnesia. In Panel A, a large lesion affects both amygdala and hippocampus and their connections with their respective circuits. In Panel B, a more restricted lesion affecting the PRPH affects inputs to both circuits including PRPH inputs to the dorsomedial thalamus.

Figure 4. Two Possible Lesion Scenarios for Diencephalic Amnesia. In Panel A, a large lesion affects both anterior and dorsomedial thalamic nuclei, thus impairing both circuits. In Panel B, a more restricted lesion affects the internal medullary lamina within the thalamus, impinging upon both the mammillothalamic tract and the ventral amygdalofugal pathway, thus impairing both circuits.

Figure 5. Two Possible Lesion Scenarios for Basal Forebrain Amnesia. In Panel A, a large lesion affects both structures within the basal forebrain (and their cholinergic projections to the two limbic circuits) as well as adjacent components of the limbic circuits themselves. In Panel B, a more restricted lesion affects cholinergic projections to both hippocampus and amygdala, thus functionally impairing both circuits.

Figure 1

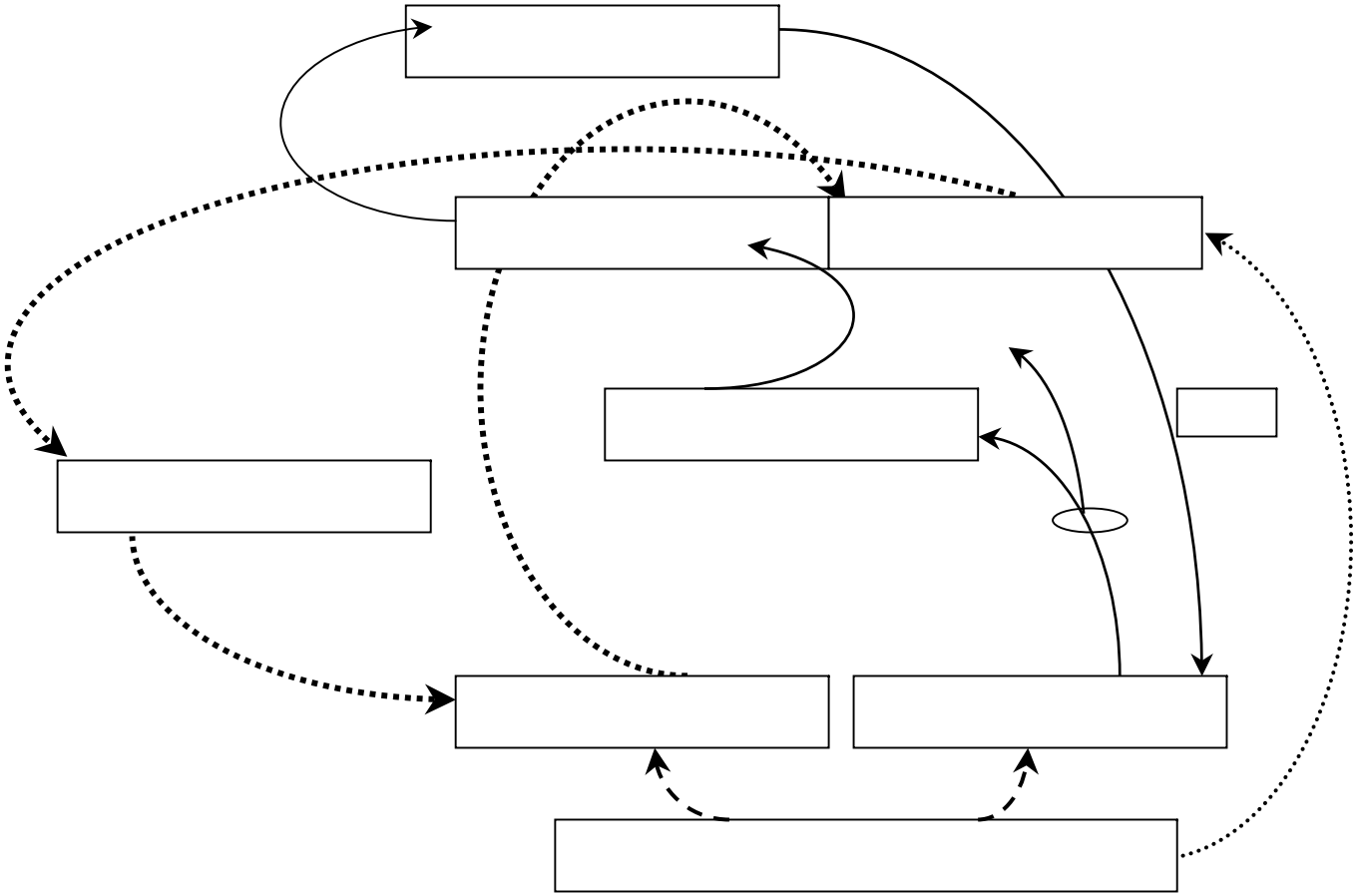
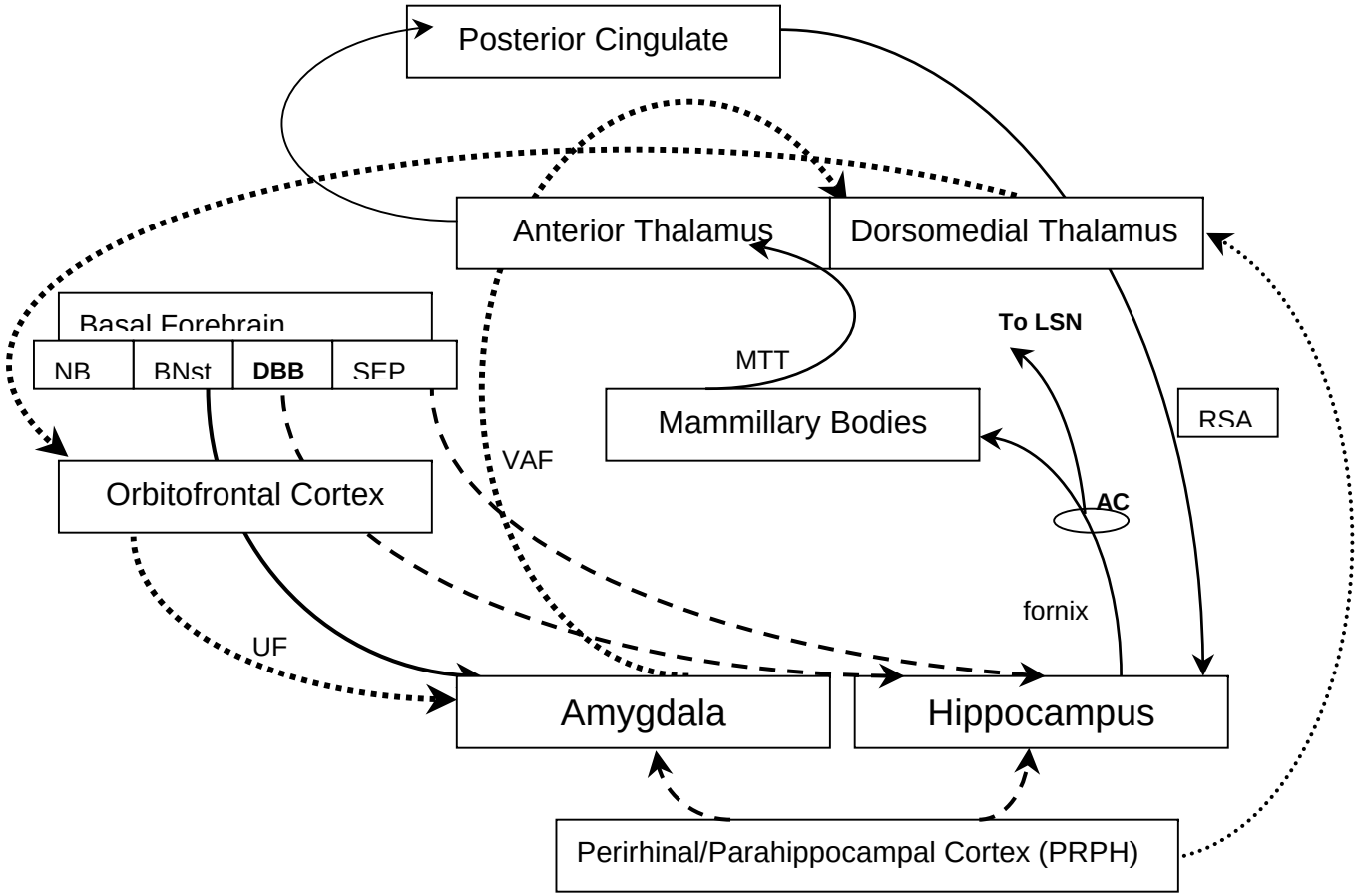


Figure 2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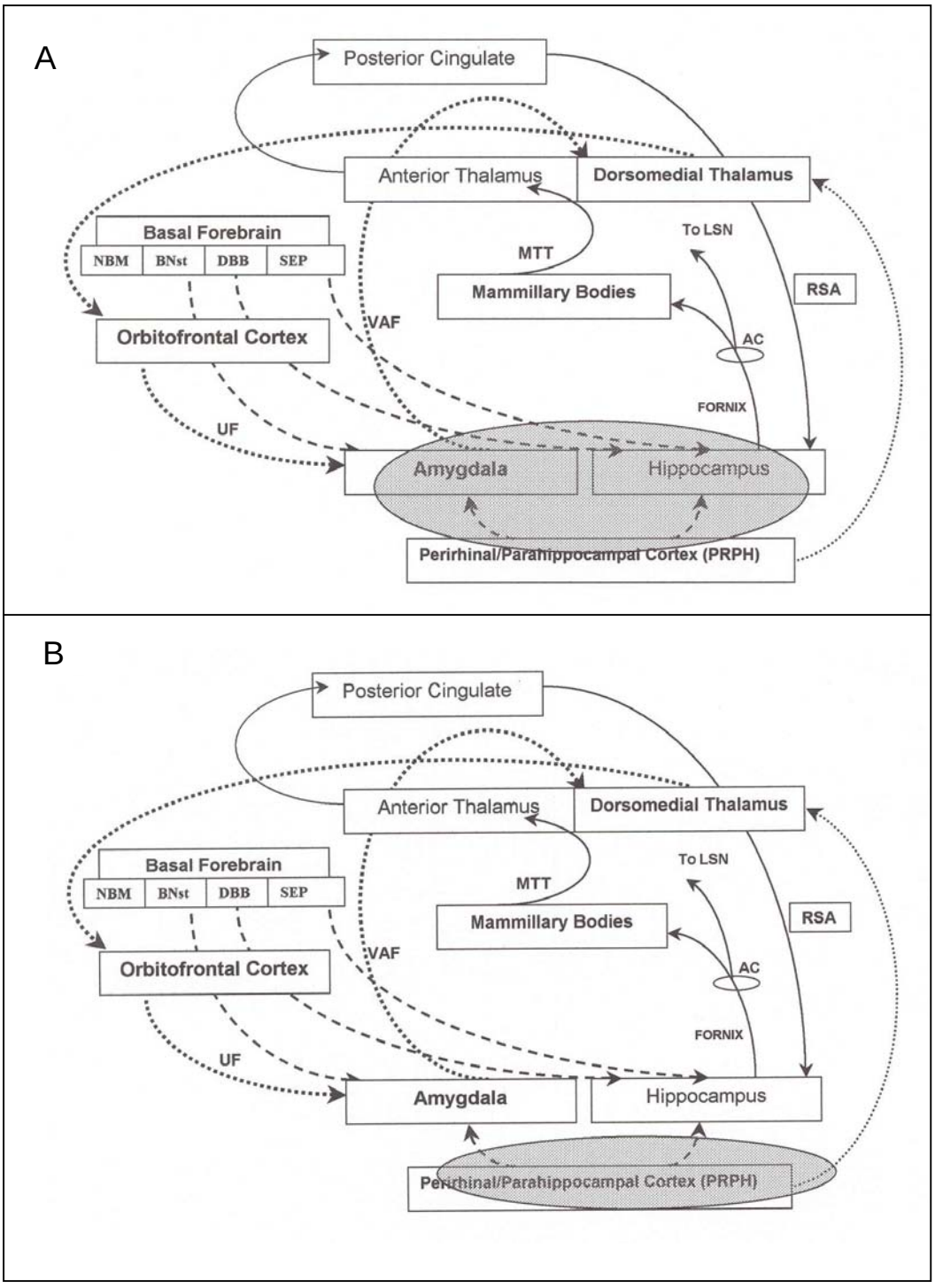
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Figure 3

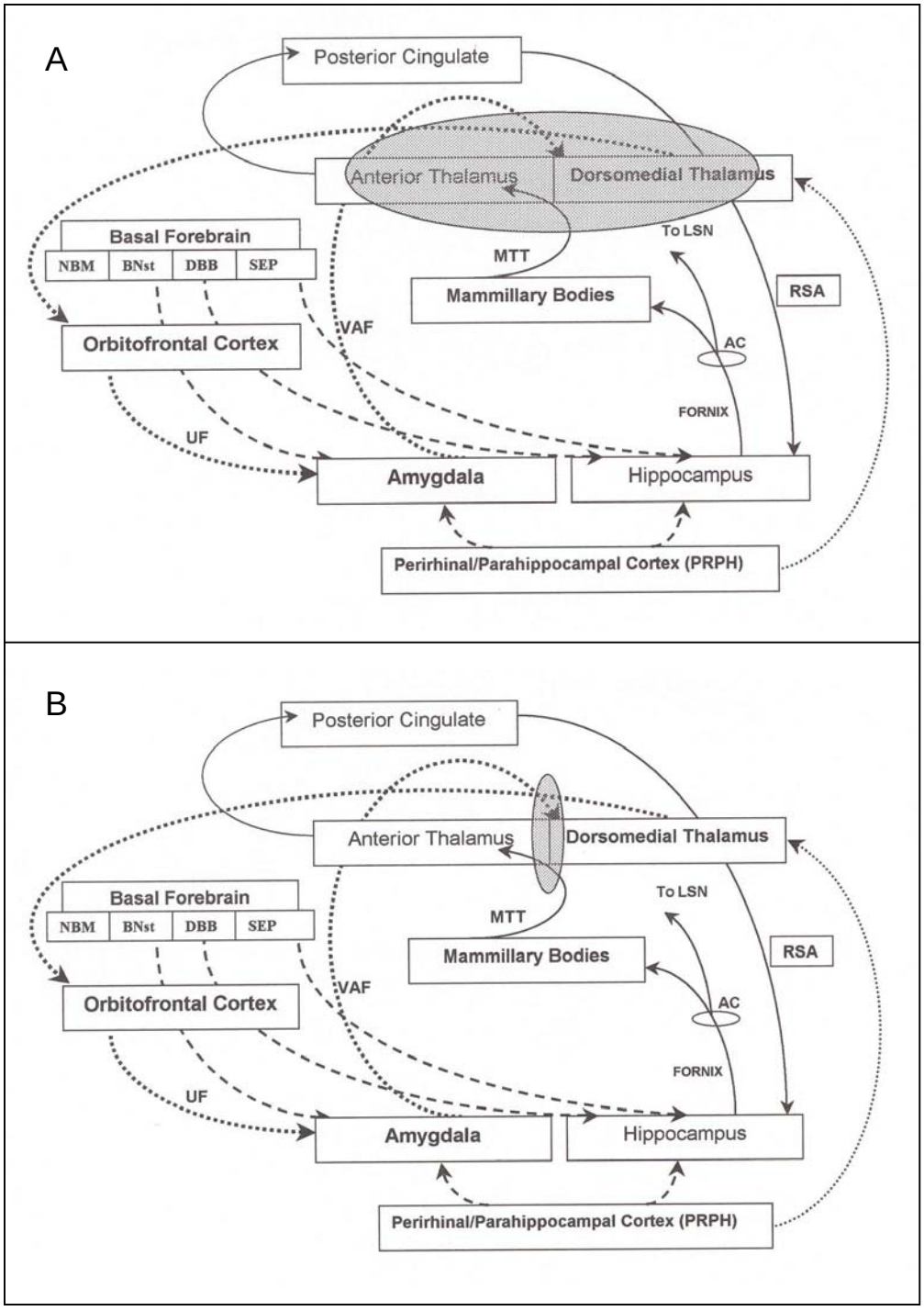
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Figure 4

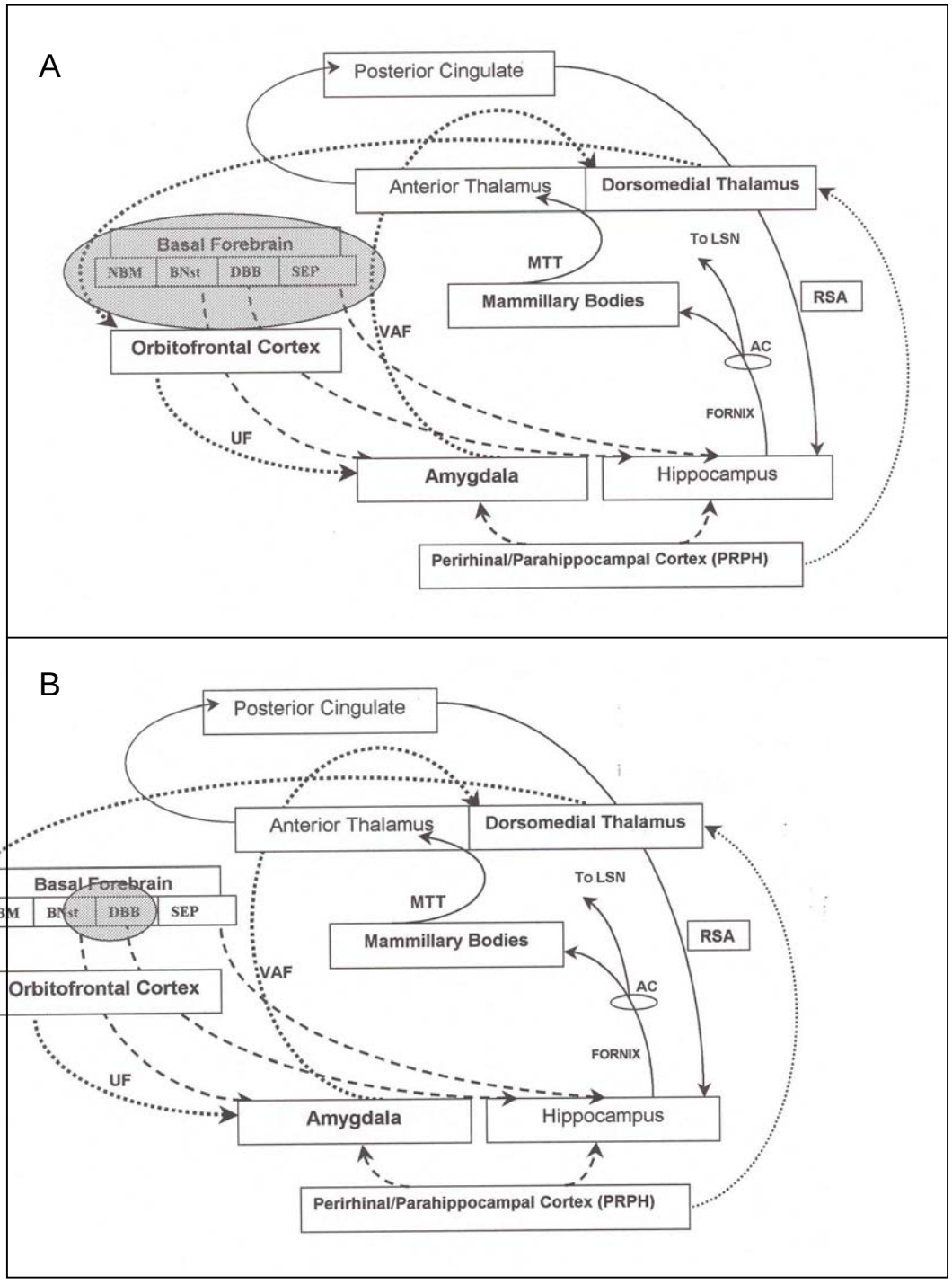
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Figure 5